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APPLICATION NUMBER: *60/461,586*
FILING DATE: *April 07, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/10737*

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PROVISIONAL APPLICATION FOR PATENT
COVER SHEET

Case No. **KALYP.007PR**
Date: April 7, 2003

United States Patent and Trademark Office
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ATTENTION: PROVISIONAL PATENT APPLICATION

Sir:

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR § 1.53(c).

For: **PYRIDINE COMPOUNDS AS MODULATORS OF PPAR AND METHODS OF TREATING METABOLIC DISORDERS**

Name of Sole Inventor: Kevin Liu
Residence Address: San Diego, California

Enclosed are:

(X) Specification in 59 pages.

(X) A check in the amount of $80 to cover the filing fee is enclosed.

(X) A return prepaid postcard.

(X) The Commissioner is hereby authorized to charge any additional fees which may be required, now or in the future, or credit any overpayment to Account No. 11-1410.

Was this invention made by an agency of the United States Government or under a contract with an agency of the United States Government?

(X) No.

( ) Yes. The name of the U.S. Government agency and the Government contract number are:

[redacted]

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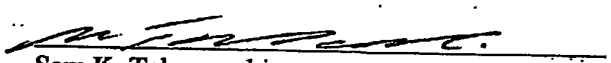
Respectfully submitted,



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CERTIFICATE OF MAILING BY "EXPRESS MAIL"

Attorney Docket No.	:	KALYP.007PR
Applicant	:	Kevin Liu
For	:	PYRIDINE COMPOUNDS AS MODULATORS OF PPAR AND METHODS OF TREATING METABOLIC DISORDERS
Attorney	:	Sam K. Tahmassebi
"Express Mail" Mailing Label No.	:	EV 230177979 US
Date of Deposit	:	April 7, 2003

I hereby certify that the accompanying

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Craig Smelter

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PYRIDINE COMPOUNDS AS MODULATORS OF PPAR AND METHODS OF TREATING METABOLIC DISORDERS

Background of the Invention

Field of the Invention

[0001] The present invention is in the field of medicinal chemistry. More specifically, the present invention relates to pyridine-derived compounds and methods for the modulation of nuclear receptor mediated processes using said compounds, in particular processes mediated by peroxisome proliferator activated receptors (PPAR).

Description of the Related Art

[0002] Peroxisome proliferators are a structurally diverse group of compounds which, when administered to mammals, elicit dramatic increases in the size and number of hepatic and renal peroxisomes, as well as concomitant increases in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes required for the β-oxidation cycle (Lazarow and Fujiki, Ann. Rev. Cell Biol. 1:489-530 (1985); Vamecq and Draye, Essays Biochem. 24:1115-225 (1989); and Nelali et al., Cancer Res. 48:5316-5324 (1988)). Chemicals included in this group are the fibrate class of hypolipidermic drugs, herbicides, and phthalate plasticizers (Reddy and Lalwani, Crit. Rev. Toxicol. 12:1-58 (1983)). Peroxisome proliferation can also be elicited by dietary or physiological factors such as a high-fat diet and cold acclimatization.

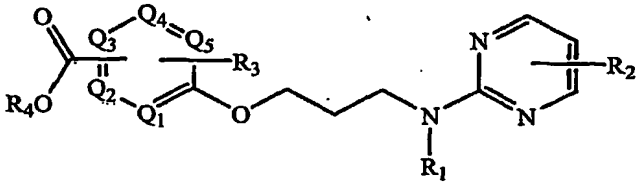
[0003] Insight into the mechanism whereby peroxisome proliferators exert their pleiotropic effects was provided by the identification of a member of the nuclear hormone receptor superfamily activated by these chemicals (Isseman and Green, Nature 347-645-650 (1990)). This receptor, termed peroxisome proliferator activated receptor alpha (PPARα), was subsequently shown to be activated by a variety of medium and long-chain fatty acids and to stimulate expression of the genes encoding rat acyl-CoA oxidase and hydratase-dehydrogenase (enzymes required for peroxisomal β-oxidation), as well as rabbit cytochrome P450 4A6, a fatty acid ω-hydroxylase (Gottlicher et al., Proc. Natl. Acad. Sci. USA 89:4653-4657 (1992); Tugwood et al., EMBO J.11:433-439 (1992); Bardot et al., Biochem. Biophys.

Res. Comm. 192:37-45 (1993); Muerhoff et al., J Biol. Chem. 267:19051-19053 (1992); and Marcus et al., Proc. Natl. Acad Sci. USA 90(12):5723-5727 (1993).

[0004] Since the discovery of PPARα, additional isoforms of PPAR have been identified, including, PPARδ (PPARβ) and PPARγ. The three isoforms of PPAR are spatially differentially expressed. Because there are three isoforms of PPAR and all of them have been shown to play important roles in energy homeostasis and other important biological processes in human body and have been shown to be important molecular targets for treatment of metabolic and other diseases (see Willson, et al. J. Med. Chem. 43: 527-550 (2000)), it is desired in the art to identify compounds which are capable of selectively interacting with only one of the PPAR isoforms or compounds which are capable of interacting with multiple PPAR isoforms. Such compounds would find a wide variety of uses, such as, for example, in the treatment or prevention of obesity, for the treatment or prevention of diabetes, dyslipidemia, metabolic syndrome X and other uses.

Summary of the Invention

[0005] Disclosed are compounds of Formula I

(I) 

and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, as described herein, as well as pharmaceutical compositions comprising the compounds, salts, esters, amides, or prodrugs thereof.

[0006] Also disclosed are methods of modulating a peroxisome proliferator-activated receptor (PPAR) function comprising contacting the PPAR with a compound of Formula I and monitoring a change in cell phenotype, cell proliferation, activity of the PPAR, or binding of the PPAR with a natural binding partner.

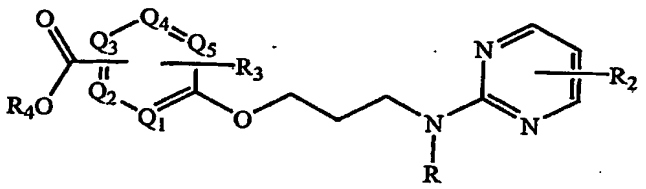
[0007] In addition, methods of inhibiting the formation of adipocytes in a mammal are disclosed, the methods comprising administering a therapeutically effective amount of a compound of Formula I to the mammal.

[0008] Methods of treating various identified diseases are also disclosed. These methods comprise administering a therapeutically effective amount of a compound of Formula I to the patient, and may further comprise the step of identifying a patient in need of treatment.

Detailed Description of the Preferred Embodiment

I. Compounds of the Invention

[0009] In the first aspect, the present invention relates to a compound of Formula I

(I) 

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

One of Q_1 - Q_5 is nitrogen and the rest are carbon, wherein said carbon is optionally substituted with hydrogen, R_3, or $-C(O)OR_4$;

R_1 - R_3 are each independently selected from the group consisting of

a) hydrogen;

b) alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino;

c) a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of

A) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

B) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; and

n1 is 0 or 1;

C) halogen or perhaloalkyl;

D) cyano;

E) nitro;

F) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

d) perhaloalkyl; and

e) halogen; and

R_4 is selected from the group consisting of hydrogen and lower alkyl.

[0010] The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutically acceptable salts may be obtained by reacting a compound of the invention with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutically acceptable salts may also be obtained by reacting a

compound of the invention with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods known in the art

[0011] The term "ester" refers to a chemical moiety with formula -COOR, where R is optionally substituted and is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon).

[0012] An "amide" is a chemical moiety with formula -C(O)NHR or -NHC(O)R, where R is are optionally substituted and is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). An amide may be an amino acid or a peptide molecule attached to a molecule of the present invention, thereby forming a prodrug.

[0013] Any amine, hydroxy, or carboxyl side chain on the compounds of the present invention can be esterified or amidified. The procedures and specific groups to be used to achieve this end is known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

[0014] A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

[0015] The term "aromatic" or "aryl" refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes both carbocyclic aryl (e.g., phenyl) and heterocyclic aryl (or "heteroaryl") groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups. The term "carbocyclic" refers to a compound which contains one or more covalently closed ring structures, and that the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon. The term "heteroaromatic" or "heteroaryl" refers to an aromatic group which contains at least one heterocyclic ring.

[0016] As used herein, the term "alkyl" refers to an aliphatic hydrocarbon group. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any alkene or alkyne moieties. The alkyl moiety may also be an "unsaturated alkyl" moiety, which means that it contains at least one alkene or alkyne moiety. An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[0017] The "alkyl" moiety may have 1 to 40 carbon atoms (whenever it appears herein, a numerical range such as "1 to 40" refers to each integer in the given range; *e.g.*, "1 to 40 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 40 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a "medium alkyl" having 1 to 20 carbon atoms. The alkyl group could also be a "lower alkyl" having 1 to 5 carbon atoms. The alkyl group of the compounds of the invention may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethly, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl.

[0018] The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Wherever a substituent is described as being "optionally substituted" that substituent may be substituted with one of the above substituents.

[0019] The substituent "R" or "R'" appearing by itself and without a number designation refers to an optionally substituted substituent selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon).

[0020] An "alkoxy" group refers to a RO- group, where R is as defined herein.

[0021] An "alkoxyalkyl" group refers to a R'OR- group, where R and R'are as defined herein.

[0022] An "alkoxyalkoxy" group refers to a ROR'O- group, where R is as defined herein.

[0023] An "mercaptyl" group refers to a RS- group, where R is as defined herein.

[0024] A "mercaptoalkyl" group refers to a R'SR- group, where R and R'are as defined herein.

[0025] A "mercaptomercaptyl" group refers to a RSR'S- group, where R is as defined herein.

[0026] An "O-carboxy" group refers to a RC(=O)O- group, where R is as defined herein.

[0027] A "C-carboxy" group refers to a -C(=O)OR groups where R is as defined herein.

[0028] An "acetyl" group refers to a -C(=O)CH_3, group.

[0029] A "trihalomethanesulfonyl" group refers to a $X_3CS(=O)_2$- group where X is a halogen.

[0030] A "cyano" group refers to a -CN group.

[0031] An "isocyanato" group refers to a -NCO group.

[0032] A "thiocyanato" group refers to a -CNS group.

[0033] An "isothiocyanato" group refers to a -NCS group.

[0034] A "sulfinyl" group refers to a -S(=O)-R group, with R as defined herein.

[0035] A "S-sulfonamido" group refers to a $-S(=O)_2NR$, group, with R as defined herein.

[0036] A "N-sulfonamido" group refers to a $RS(=O)_2NH$- group with R as defined herein.

[0037] A "trihalomethanesulfonamido" group refers to a $X_3CS(=O)_2NR$- group with X and R as defined herein.

[0038] An "O-carbamyl" group refers to a -OC(=O)-NR, group-with R as defined herein.

[0039] An "N-carbamyl" group refers to a ROC(=O)NH- group, with R as defined herein.

[0040] An "O-thiocarbamyl" group refers to a -OC(=S)-NR, group with R as defined herein.

[0041] An "N-thiocarbamyl" group refers to an ROC(=S)NH- group, with R as defined herein.

[0042] A "C-amido" group refers to a $-C(=O)-NR_2$ group with R as defined herein.

[0043] An "N-amido" group refers to a RC(=O)NH- group, with R as defined herein.

[0044] The term "perhaloalkyl" refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[0045] The term "alkylene" refers to an alkyl group that is substituted at two ends (i.e., a diradical). Thus, methylene ($-CH_2-$) ethylene ($-CH_2CH_2-$), and propylene (-

$CH_2CH_2CH_2$-) are examples of alkylene groups. Similarly, "alkenylene" and "alkynylene" groups refer to diradical alkene and alkyne moieties, respectively.

[0046] Unless otherwise indicated, when a substituent is deemed to be "optionally substituted," it is meant that the substituent is a group that may be substituted with one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, above.

[0047] In certain embodiments, in the compound of Formula I, R_1 may be alkyl, optionally substituted with one or more optionally substituted carbocyclic or heterocyclic rings. The alkyl may be a lower alkyl, which may be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl. In some embodiments, the carbocyclic ring phenyl, which may be optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino. In some embodiments the substituent is perhaloalkyl, which may be trifluoromethyl. In certain embodiments R_1 is 2,4-bis(trifluoromethyl)phenyl.

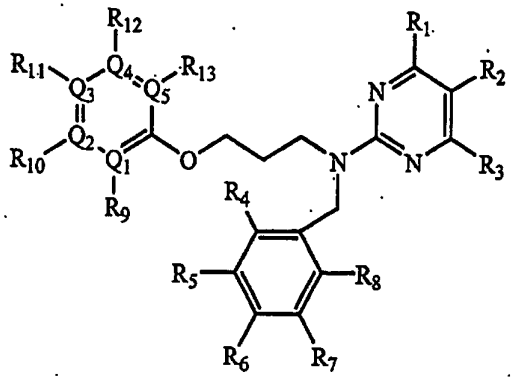
[0048] In some embodiments, R_2 is optionally substituted alkyl. In certain embodiments, the alkyl is a lower alkyl, which may be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl. In some embodiments, R_2 is ethyl.

[0049] Some embodiments include those in which R_3 is hydrogen, halogen, or optionally substituted alkyl. The alkyl may be a lower alkyl, which may be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl. In some embodiments R_3 is methyl, whereas in other embodiments, R_3 is hydrogen. In other embodiments, R_3 may be halogen, which may be selected from the group consisting of fluoro, chloro, bromo, and iodo. In some embodiments R_3 is chloro.

[0050] In some embodiments, R_4 is hydrogen or optionally substituted alkyl. The alkyl may be a lower alkyl, which may be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl. In certain embodiments, R_4 is hydrogen.

[0051] In another aspect, the present invention relates to one or more compound set forth in Table 1, below, or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

Table 1



Comp'd No.	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}	R_{12}	R_{13}	Q_1	Q_2	Q_3	Q_4	Q_5
KP001	H	H	H	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP002	H	H	H	H	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP003	H	H	H	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP004	H	H	H	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP005	H	H	H	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP006	H	H	H	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP007	H	H	H	H	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP008	H	H	H	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP009	H	H	H	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP010	H	H	H	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP011	$-CH_3$	H	H	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP012	$-CH_3$	H	H	H	H	N/A	H	-COOH	H	H	N	C	C	C	C

Complex No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_{12}	R_{11}	Q_1	Q_2	Q_3	Q_4	Q_5
KP013	$-CH_3$	H	H	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP014	$-CH_3$	H	H	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP015	$-CH_3$	H	H	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP016	$-CH_3$	H	H	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP017	$-CH_3$	H	H	H	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP018	$-CH_3$	H	H	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP019	$-CH_3$	H	H	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP020	$-CH_3$	H	H	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP021	H	$-CH_3$	H	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP022	H	$-CH_3$	H	H	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP023	H	$-CH_3$	H	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP024	H	$-CH_3$	H	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP025	H	$-CH_3$	H	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP026	H	$-CH_3$	H	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP027	H	$-CH_3$	H	H	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP028	H	$-CH_3$	H	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP029	H	$-CH_3$	H	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP030	H	$-CH_3$	H	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP031	H	H	$-CH_3$	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP032	H	H	$-CH_3$	H	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP033	H	H	$-CH_3$	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP034	H	H	$-CH_3$	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP035	H	H	$-CH_3$	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP036	H	H	$-CH_3$	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP037	H	H	$-CH_3$	H	H	H	N/A	H	-COOH	H	C	N	C	C	C

Compd. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}	R_{12}	R_{13}	Q_1	Q_2	Q_3	Q_4	Q_5
KP038	H	H	$-CH_3$	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP039	H	H	$-CH_3$	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP040	H	H	$-CH_3$	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP041	$-CH_3$	$-CH_3$	H	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP042	$-CH_3$	$-CH_3$	H	H	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP043	$-CH_3$	$-CH_3$	H	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP044	$-CH_3$	$-CH_3$	H	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP045	$-CH_3$	$-CH_3$	H	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP046	$-CH_3$	$-CH_3$	H	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP047	$-CH_3$	$-CH_3$	H	H	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP048	$-CH_3$	$-CH_3$	H	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP049	$-CH_3$	$-CH_3$	H	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP050	$-CH_3$	$-CH_3$	H	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP051	$-CH_3$	H	$-CH_3$	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP052	$-CH_3$	H	$-CH_3$	H	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP053	$-CH_3$	H	$-CH_3$	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP054	$-CH_3$	H	$-CH_3$	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP055	$-CH_3$	H	$-CH_3$	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP056	$-CH_3$	H	$-CH_3$	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP057	$-CH_3$	H	$-CH_3$	H	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP058	$-CH_3$	H	$-CH_3$	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP059	$-CH_3$	H	$-CH_3$	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP060	$-CH_3$	H	$-CH_3$	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP061	$-CH_3$	H	H	$-CH_3$	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP062	$-CH_3$	H	H	$-CH_3$	H	N/A	H	-COOH	H	H	N	C	C	C	C

Compd. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}	Q_1	Q_2	Q_3	Q_4	Q_5
KP063	$-CH_3$	H	H	$-CH_3$	H	N/A	H	H	-COOH	H	N	C	C	C	C	C
KP064	$-CH_3$	H	H	$-CH_3$	H	N/A	H	H	H	-COOH	N	C	C	C	C	C
KP065	$-CH_3$	H	H	$-CH_3$	H	-COOH	N/A	H	H	H	C	N	C	C	C	C
KP066	$-CH_3$	H	H	$-CH_3$	H	H	N/A	-COOH	H	H	C	N	C	C	C	C
KP067	$-CH_3$	H	H	$-CH_3$	H	H	N/A	H	-COOH	H	C	N	C	C	C	C
KP068	$-CH_3$	H	H	$-CH_3$	H	H	N/A	H	H	-COOH	C	N	C	C	C	C
KP069	$-CH_3$	H	H	$-CH_3$	H	-COOH	H	N/A	H	H	C	C	N	C	C	C
KP070	$-CH_3$	H	H	$-CH_3$	H	H	-COOH	N/A	H	H	C	C	N	C	C	C
KP071	$-CH_3$	H	H	H	$-CH_3$	N/A	-COOH	H	H	H	N	C	C	C	C	C
KP072	$-CH_3$	H	H	H	$-CH_3$	N/A	H	-COOH	H	H	N	C	C	C	C	C
KP073	$-CH_3$	H	H	H	$-CH_3$	N/A	H	H	-COOH	H	N	C	C	C	C	C
KP074	$-CH_3$	H	H	H	$-CH_3$	N/A	H	H	H	-COOH	N	C	C	C	C	C
KP075	$-CH_3$	H	H	H	$-CH_3$	-COOH	N/A	H	H	H	C	N	C	C	C	C
KP076	$-CH_3$	H	H	H	$-CH_3$	H	N/A	-COOH	H	H	C	N	C	C	C	C
KP077	$-CH_3$	H	H	H	$-CH_3$	H	N/A	H	-COOH	H	C	N	C	C	C	C
KP078	$-CH_3$	H	H	H	$-CH_3$	H	N/A	H	H	-COOH	C	N	C	C	C	C
KP079	$-CH_3$	H	H	H	$-CH_3$	-COOH	H	N/A	H	H	C	C	N	C	C	C
KP080	$-CH_3$	H	H	H	$-CH_3$	H	-COOH	N/A	H	H	C	C	N	C	C	C
KP081	H	$-CH_3$	$-CH_3$	H	H	N/A	-COOH	H	H	H	N	C	C	C	C	C
KP082	H	$-CH_3$	$-CH_3$	H	H	N/A	H	-COOH	H	H	N	C	C	C	C	C
KP083	H	$-CH_3$	$-CH_3$	H	H	N/A	H	H	-COOH	H	N	C	C	C	C	C
KP084	H	$-CH_3$	$-CH_3$	H	H	N/A	H	H	H	-COOH	N	C	C	C	C	C
KP085	H	$-CH_3$	$-CH_3$	H	H	-COOH	N/A	H	H	H	C	N	C	C	C	C
KP086	H	$-CH_3$	$-CH_3$	H	H	H	N/A	-COOH	H	H	C	N	C	C	C	C
KP087	H	$-CH_3$	$-CH_3$	H	H	H	N/A	H	-COOH	H	C	N	C	C	C	C

Compound No.	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}	R_{12}	R_{13}	Q_1	Q_2	Q_3	Q_4	Q_5
KP088	H	$-CH_3$	$-CH_3$	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP089	H	$-CH_3$	$-CH_3$	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP090	H	$-CH_3$	$-CH_3$	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP091	H	$-CH_3$	H	$-CH_3$	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP092	H	$-CH_3$	H	$-CH_3$	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP093	H	$-CH_3$	H	$-CH_3$	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP094	H	$-CH_3$	H	$-CH_3$	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP095	H	$-CH_3$	H	$-CH_3$	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP096	H	$-CH_3$	H	$-CH_3$	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP097	H	$-CH_3$	H	$-CH_3$	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP098	H	$-CH_3$	H	$-CH_3$	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP099	H	$-CH_3$	H	$-CH_3$	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP100	H	$-CH_3$	H	$-CH_3$	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP101	$-CF_3$	H	H	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP102	$-CF_3$	H	H	H	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP103	$-CF_3$	H	H	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP104	$-CF_3$	H	H	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP105	$-CF_3$	H	H	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP106	$-CF_3$	H	H	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP107	$-CF_3$	H	H	H	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP108	$-CF_3$	H	H	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP109	$-CF_3$	H	H	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP110	$-CF_3$	H	H	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP111	H	$-CF_3$	H	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP112	H	$-CF_3$	H	H	H	N/A	H	-COOH	H	H	N	C	C	C	C

Comp. No.	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}	Q_1	Q_2	Q_3	Q_4	Q_5
KP113	H	$-CF_3$	H	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP114	H	$-CF_3$	H	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP115	H	$-CF_3$	H	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP116	H	$-CF_3$	H	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP117	H	$-CF_3$	H	H	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP118	H	$-CF_3$	H	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP119	H	$-CF_3$	H	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP120	H	$-CF_3$	H	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP121	H	H	$-CF_3$	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP122	H	H	$-CF_3$	H	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP123	H	H	$-CF_3$	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP124	H	H	$-CF_3$	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP125	H	H	$-CF_3$	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP126	H	H	$-CF_3$	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP127	H	H	$-CF_3$	H	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP128	H	H	$-CF_3$	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP129	H	H	$-CF_3$	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP130	H	H	$-CF_3$	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP131	$-CF_3$	$-CF_3$	H	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP132	$-CF_3$	$-CF_3$	H	H	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP133	$-CF_3$	$-CF_3$	H	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP134	$-CF_3$	$-CF_3$	H	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP135	$-CF_3$	$-CF_3$	H	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP136	$-CF_3$	$-CF_3$	H	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP137	$-CF_3$	$-CF_3$	H	H	H	H	N/A	H	-COOH	H	C	N	C	C	C

Compd No	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	Q_1	Q_2	Q_3	Q_4	Q_5
KP138	$-CF_3$	$-CF_3$	H	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP139	$-CF_3$	$-CF_3$	H	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP140	$-CF_3$	$-CF_3$	H	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP141	$-CF_3$	H	$-CF_3$	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP142	$-CF_3$	H	$-CF_3$	H	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP143	$-CF_3$	H	$-CF_3$	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP144	$-CF_3$	H	$-CF_3$	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP145	$-CF_3$	H	$-CF_3$	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP146	$-CF_3$	H	$-CF_3$	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP147	$-CF_3$	H	$-CF_3$	H	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP148	$-CF_3$	H	$-CF_3$	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP149	$-CF_3$	H	$-CF_3$	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP150	$-CF_3$	H	$-CF_3$	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP151	$-CF_3$	H	H	$-CF_3$	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP152	$-CF_3$	H	H	$-CF_3$	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP153	$-CF_3$	H	H	$-CF_3$	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP154	$-CF_3$	H	H	$-CF_3$	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP155	$-CF_3$	H	H	$-CF_3$	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP156	$-CF_3$	H	H	$-CF_3$	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP157	$-CF_3$	H	H	$-CF_3$	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP158	$-CF_3$	H	H	$-CF_3$	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP159	$-CF_3$	H	H	$-CF_3$	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP160	$-CF_3$	H	H	$-CF_3$	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP161	$-CF_3$	H	H	H	$-CF_3$	N/A	-COOH	H	H	H	N	C	C	C	C
KP162	$-CF_3$	H	H	H	$-CF_3$	N/A	H	-COOH	H	H	N	C	C	C	C

Comp'd No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}	Q_1	Q_2	Q_3	Q_4	Q_5
KP163	$-CF_3$	H	H	H	$-CF_3$	N/A	H	H	-COOH	H	N	C	C	C	C
KP164	$-CF_3$	H	H	H	$-CF_3$	N/A	H	H	H	-COOH	N	C	C	C	C
KP165	$-CF_3$	H	H	H	$-CF_3$	-COOH	N/A	H	H	H	C	N	C	C	C
KP166	$-CF_3$	H	H	H	$-CF_3$	H	N/A	-COOH	H	H	C	N	C	C	C
KP167	$-CF_3$	H	H	H	$-CF_3$	H	N/A	H	-COOH	H	C	N	C	C	C
KP168	$-CF_3$	H	H	H	$-CF_3$	H	N/A	H	H	-COOH	C	N	C	C	C
KP169	$-CF_3$	H	H	H	$-CF_3$	-COOH	H	N/A	H	H	C	C	N	C	C
KP170	$-CF_3$	H	H	H	$-CF_3$	H	-COOH	N/A	H	H	C	C	N	C	C
KP171	H	$-CF_3$	$-CF_3$	H	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP172	H	$-CF_3$	$-CF_3$	H	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP173	H	$-CF_3$	$-CF_3$	H	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP174	H	$-CF_3$	$-CF_3$	H	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP175	H	$-CF_3$	$-CF_3$	H	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP176	H	$-CF_3$	$-CF_3$	H	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP177	H	$-CF_3$	$-CF_3$	H	H	H	N/A	H	-COOH	H	C	N	C	C	C
KP178	H	$-CF_3$	$-CF_3$	H	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP179	H	$-CF_3$	$-CF_3$	H	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP180	H	$-CF_3$	$-CF_3$	H	H	H	-COOH	N/A	H	H	C	C	N	C	C
KP181	H	$-CF_3$	H	$-CF_3$	H	N/A	-COOH	H	H	H	N	C	C	C	C
KP182	H	$-CF_3$	H	$-CF_3$	H	N/A	H	-COOH	H	H	N	C	C	C	C
KP183	H	$-CF_3$	H	$-CF_3$	H	N/A	H	H	-COOH	H	N	C	C	C	C
KP184	H	$-CF_3$	H	$-CF_3$	H	N/A	H	H	H	-COOH	N	C	C	C	C
KP185	H	$-CF_3$	H	$-CF_3$	H	-COOH	N/A	H	H	H	C	N	C	C	C
KP186	H	$-CF_3$	H	$-CF_3$	H	H	N/A	-COOH	H	H	C	N	C	C	C
KP187	H	$-CF_3$	H	$-CF_3$	H	H	N/A	H	-COOH	H	C	N	C	C	C

Compd. No.	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}	R_{12}	R_{13}	Q_1	Q_2	Q_3	Q_4	Q_5
KP188	H	$-CF_3$	H	$-CF_3$	H	H	N/A	H	H	-COOH	C	N	C	C	C
KP189	H	$-CF_3$	H	$-CF_3$	H	-COOH	H	N/A	H	H	C	C	N	C	C
KP190	H	$-CF_3$	H	$-CF_3$	H	H	-COOH	N/A	H	H	C	C	N	C	C

[0052] In addition to the KP001 through KP190 compounds listed in Table 1, above, aspects of the present invention include the following compounds:

KP001-1ET through KP190-1ET, in which R_1 is an ethyl group while the remainder of the substituents remain the same as KP001 through KP190;

KP001-2ET through KP190-2ET, in which R_2 is an ethyl group while the remainder of the substituents remain the same as KP001 through KP190;

KP006-9CL through KP008-9CL, KP010-9CL, KP016-9CL through KP018-9CL, KP020-9CL, KP026-9CL through KP028-9CL, KP030-9CL, KP036-9CL through KP038-9CL, KP040-9CL, KP046-9CL through KP048-9CL, KP050-9CL, KP056-9CL through KP058-9CL, KP060-9CL, KP066-9CL through KP068-9CL, KP070-9CL, KP076-9CL through KP078-9CL, KP080-9CL, KP086-9CL through KP088-9CL, KP090-9CL, KP096-9CL through KP098-9CL, KP100-9CL, KP106-9CL through KP108-9CL, KP110-9CL, KP116-9CL through KP118-9CL, KP120-9CL, KP126-9CL through KP128-9CL, KP130-9CL, KP136-9CL through KP138-9CL, KP140-9CL, KP146-9CL through KP148-9CL, KP150-9CL, KP156-9CL through KP158-9CL, KP160-9CL, KP166-9CL through KP168-9CL, KP170-9CL, KP176-9CL through KP178-9CL, KP180-9CL, KP186-9CL through KP188-9CL, KP190-9CL, KP006-1ET-9CL through KP008-1ET-9CL, KP010-1ET-9CL, KP016-1ET-9CL through KP018-1ET-9CL, KP020-1ET-9CL, KP026-1ET-9CL through KP028-1ET-9CL, KP030-1ET-9CL, KP036-1ET-9CL through KP038-1ET-9CL, KP040-1ET-9CL, KP046-1ET-9CL through KP048-1ET-9CL, KP050-1ET-9CL, KP056-1ET-9CL through KP058-1ET-9CL, KP060-1ET-9CL, KP066-1ET-9CL through KP068-1ET-9CL, KP070-1ET-9CL, KP076-1ET-9CL through KP078-1ET-9CL, KP080-1ET-9CL, KP086-1ET-9CL through KP088-1ET-9CL, KP090-1ET-9CL, KP096-1ET-9CL through KP098-1ET-9CL, KP100-1ET-9CL, KP106-1ET-9CL through KP108-1ET-9CL, KP110-1ET-9CL, KP116-1ET-9CL through KP118-1ET-9CL, KP120-1ET-9CL, KP126-1ET-9CL through KP128-1ET-9CL, KP130-1ET-9CL, KP136-1ET-9CL through KP138-1ET-9CL, KP140-1ET-9CL, KP146-1ET-9CL through KP148-1ET-9CL, KP150-1ET-9CL, KP156-1ET-9CL through KP158-1ET-9CL, KP160-1ET-9CL, KP166-1ET-9CL through KP168-1ET-9CL, KP170-1ET-9CL, KP176-1ET-9CL through KP178-1ET-9CL, KP180-1ET-9CL, KP186-1ET-9CL through KP188-1ET-9CL, KP190-1ET-9CL, KP006-2ET-9CL through KP008-

2ET-9CL, KP010-2ET-9CL, KP016-2ET-9CL through KP018-2ET-9CL, KP020-2ET-9CL, KP026-2ET-9CL through KP028-2ET-9CL, KP030-2ET-9CL, KP036-2ET-9CL through KP038-2ET-9CL, KP040-2ET-9CL, KP046-2ET-9CL through KP048-2ET-9CL, KP050-2ET-9CL, KP056-2ET-9CL through KP058-2ET-9CL, KP060-2ET-9CL, KP066-2ET-9CL through KP068-2ET-9CL, KP070-2ET-9CL, KP076-2ET-9CL through KP078-2ET-9CL, KP080-2ET-9CL, KP086-2ET-9CL through KP088-2ET-9CL, KP090-2ET-9CL, KP096-2ET-9CL through KP098-2ET-9CL, KP100-2ET-9CL, KP106-2ET-9CL through KP108-2ET-9CL, KP110-2ET-9CL, KP116-2ET-9CL through KP118-2ET-9CL, KP120-2ET-9CL, KP126-2ET-9CL through KP128-2ET-9CL, KP130-2ET-9CL, KP136-2ET-9CL through KP138-2ET-9CL, KP140-2ET-9CL, KP146-2ET-9CL through KP148-2ET-9CL, KP150-2ET-9CL, KP156-2ET-9CL through KP158-2ET-9CL, KP160-2ET-9CL, KP166-2ET-9CL through KP168-2ET-9CL, KP170-2ET-9CL, KP176-2ET-9CL through KP178-2ET-9CL, KP180-2ET-9CL, KP186-2ET-9CL through KP188-2ET-9CL, and KP190-2ET-9CL, in which R_9 is a chloro while the remainder of the substituents remain the same as the corresponding compound in Table 1;

KP002-10CL through KP004-10CL, KP009-10CL, KP012-10CL through KP014-10CL, KP019-10CL, KP022-10CL through KP024-10CL, KP029-10CL, KP032-10CL through KP034-10CL, KP039-10CL, KP042-10CL through KP044-10CL, KP049-10CL, KP052-10CL through KP054-10CL, KP059-10CL, KP062-10CL through KP064-10CL, KP069-10CL, KP072-10CL through KP074-10CL, KP079-10CL, KP082-10CL through KP084-10CL, KP089-10CL, KP092-10CL through KP094-10CL, KP099-10CL, KP102-10CL through KP104-10CL, KP109-10CL, KP112-10CL through KP114-10CL, KP119-10CL, KP122-10CL through KP124-10CL, KP129-10CL, KP132-10CL through KP134-10CL, KP139-10CL, KP142-10CL through KP144-10CL, KP149-10CL, KP152-10CL through KP154-10CL, KP159-10CL, KP166-10CL through KP164-10CL, KP169-10CL, KP172-10CL through KP174-10CL, KP179-10CL, KP182-10CL through KP184-10CL, KP189-10CL, KP002-1ET-10CL through KP004-1ET-10CL, KP009-1ET-10CL, KP012-1ET-10CL through KP014-1ET-10CL, KP019-1ET-10CL, KP022-1ET-10CL through KP024-1ET-10CL, KP029-1ET-10CL, KP032-1ET-10CL through KP034-1ET-10CL, KP039-1ET-10CL, KP042-1ET-10CL through KP044-1ET-10CL, KP049-1ET-10CL,

KP052-1ET-10CL through KP054-1ET-10CL, KP059-1ET-10CL, KP062-1ET-10CL through KP064-1ET-10CL, KP069-1ET-10CL, KP072-1ET-10CL through KP074-1ET-10CL, KP079-1ET-10CL, KP082-1ET-10CL through KP084-1ET-10CL, KP089-1ET-10CL, KP092-1ET-10CL through KP094-1ET-10CL, KP099-1ET-10CL, KP102-1ET-10CL through KP104-1ET-10CL, KP109-1ET-10CL, KP112-1ET-10CL through KP114-1ET-10CL, KP119-1ET-10CL, KP122-1ET-10CL through KP124-1ET-10CL, KP129-1ET-10CL, KP132-1ET-10CL through KP134-1ET-10CL, KP139-1ET-10CL, KP142-1ET-10CL through KP144-1ET-10CL, KP149-1ET-10CL, KP152-1ET-10CL through KP154-1ET-10CL, KP159-1ET-10CL, KP162-1ET-10CL through KP164-1ET-10CL, KP169-1ET-10CL, KP172-1ET-10CL through KP174-1ET-10CL, KP179-1ET-10CL, KP182-1ET-10CL through KP184-1ET-10CL, KP189-1ET-10CL, KP002-2ET-10CL through KP004-2ET-10CL, KP009-2ET-10CL, KP012-2ET-10CL through KP014-2ET-10CL, KP019-2ET-10CL, KP022-2ET-10CL through KP024-2ET-10CL, KP029-2ET-10CL, KP032-2ET-10CL through KP034-2ET-10CL, KP039-2ET-10CL, KP042-2ET-10CL through KP044-2ET-10CL, KP049-2ET-10CL, KP052-2ET-10CL through KP054-2ET-10CL, KP059-2ET-10CL, KP062-2ET-10CL through KP064-2ET-10CL, KP069-2ET-10CL, KP072-2ET-10CL through KP074-2ET-10CL, KP079-2ET-10CL, KP082-2ET-10CL through KP084-2ET-10CL, KP089-2ET-10CL, KP092-2ET-10CL through KP094-2ET-10CL, KP099-2ET-10CL, KP102-2ET-10CL through KP104-2ET-10CL, KP109-2ET-10CL, KP112-2ET-10CL through KP114-2ET-10CL, KP119-2ET-10CL, KP122-2ET-10CL through KP124-2ET-10CL, KP129-2ET-10CL, KP132-2ET-10CL through KP134-2ET-10CL, KP139-2ET-10CL, KP142-2ET-10CL through KP144-2ET-10CL, KP149-2ET-10CL, KP152-2ET-10CL through KP154-2ET-10CL, KP159-2ET-10CL, KP162-2ET-10CL through KP164-2ET-10CL, KP169-2ET-10CL, KP172-2ET-10CL through KP174-2ET-10CL, KP179-2ET-10CL, KP182-2ET-10CL through KP184-2ET-10CL, and KP189-2ET-10CL, in which R_{10} is a chloro while the remainder of the substituents remain the same as the corresponding compound in Table 1;

KP001-11CL, KP003-11CL through KP005-11CL, KP007-11CL, KP008-11CL, KP011-11CL, KP013-11CL through KP015-11CL, KP017-11CL, KP018-11CL, KP021-11CL, KP023-11CL through KP025-11CL, KP027-11CL, KP028-11CL, KP031-11CL,

KP033-11CL through KP035-11CL, KP037-11CL, KP038-11CL, KP041-11CL, KP043-11CL through KP045-11CL, KP047-11CL, KP048-11CL, KP051-11CL, KP053-11CL through KP055-11CL, KP057-11CL, KP058-11CL, KP061-11CL, KP063-11CL through KP065-11CL, KP067-11CL, KP068-11CL, KP071-11CL, KP073-11CL through KP075-11CL, KP077-11CL, KP078-11CL, KP081-11CL, KP083-11CL through KP085-11CL, KP087-11CL, KP088-11CL, KP091-11CL, KP093-11CL through KP095-11CL, KP097-11CL, KP098-11CL, KP101-11CL, KP103-11CL through KP105-11CL, KP107-11CL, KP108-11CL, KP111-11CL, KP113-11CL through KP115-11CL, KP117-11CL, KP118-11CL, KP121-11CL, KP123-11CL through KP125-11CL, KP127-11CL, KP128-11CL, KP131-11CL, KP133-11CL through KP135-11CL, KP137-11CL, KP138-11CL, KP141-11CL, KP143-11CL through KP145-11CL, KP147-11CL, KP148-11CL, KP151-11CL, KP153-11CL through KP155-11CL, KP157-11CL, KP158-11CL, KP161-11CL, KP163-11CL through KP165-11CL, KP167-11CL, KP168-11CL, KP171-11CL, KP173-11CL through KP175-11CL, KP177-11CL, KP178-11CL, KP181-11CL, KP183-11CL through KP185-11CL, KP187-11CL, KP188-11CL, KP001-1ET-11CL, KP003-1ET-11CL through KP005-1ET-11CL, KP007-1ET-11CL, KP008-1ET-11CL, KP011-1ET-11CL, KP013-1ET-11CL through KP015-1ET-11CL, KP017-1ET-11CL, KP018-1ET-11CL, KP021-1ET-11CL, KP023-1ET-11CL through KP025-1ET-11CL, KP027-1ET-11CL, KP028-1ET-11CL, KP031-1ET-11CL, KP033-1ET-11CL through KP035-1ET-11CL, KP037-1ET-11CL, KP038-1ET-11CL, KP041-1ET-11CL, KP043-1ET-11CL through KP045-1ET-11CL, KP047-1ET-11CL, KP048-1ET-11CL, KP051-1ET-11CL, KP053-1ET-11CL through KP055-1ET-11CL, KP057-1ET-11CL, KP058-1ET-11CL, KP061-1ET-11CL, KP063-1ET-11CL through KP065-1ET-11CL, KP067-1ET-11CL, KP068-1ET-11CL, KP071-1ET-11CL, KP073-1ET-11CL through KP075-1ET-11CL, KP077-1ET-11CL, KP078-1ET-11CL, KP081-1ET-11CL, KP083-1ET-11CL through KP085-1ET-11CL, KP087-1ET-11CL, KP088-1ET-11CL, KP091-1ET-11CL, KP093-1ET-11CL through KP095-1ET-11CL, KP097-1ET-11CL, KP098-1ET-11CL, KP101-1ET-11CL, KP103-1ET-11CL through KP105-1ET-11CL, KP107-1ET-11CL, KP108-1ET-11CL, KP111-1ET-11CL, KP113-1ET-11CL through KP115-1ET-11CL, KP117-1ET-11CL, KP118-1ET-11CL, KP121-1ET-11CL, KP123-1ET-11CL through KP125-1ET-11CL, KP127-1ET-11CL, KP128-1ET-11CL,

KP131-1ET-11CL, KP133-1ET-11CL through KP135-1ET-11CL, KP137-1ET-11CL, KP138-1ET-11CL, KP141-1ET-11CL, KP143-1ET-11CL through KP145-1ET-11CL, KP147-1ET-11CL, KP148-1ET-11CL, KP151-1ET-11CL, KP153-1ET-11CL through KP155-1ET-11CL, KP157-1ET-11CL, KP158-1ET-11CL, KP161-1ET-11CL, KP163-1ET-11CL through KP165-1ET-11CL, KP167-1ET-11CL, KP168-1ET-11CL, KP171-1ET-11CL, KP173-1ET-11CL through KP175-1ET-11CL, KP177-1ET-11CL, KP178-1ET-11CL, KP181-1ET-11CL, KP183-1ET-11CL through KP185-1ET-11CL, KP187-1ET-11CL, KP188-1ET-11CL, KP001-2ET-11CL, KP003-2ET-11CL through KP005-2ET-11CL, KP007-2ET-11CL, KP008-2ET-11CL, KP011-2ET-11CL, KP013-2ET-11CL through KP015-2ET-11CL, KP017-2ET-11CL, KP018-2ET-11CL, KP021-2ET-11CL, KP023-2ET-11CL through KP025-2ET-11CL, KP027-2ET-11CL, KP028-2ET-11CL, KP031-2ET-11CL, KP033-2ET-11CL through KP035-2ET-11CL, KP037-2ET-11CL, KP038-2ET-11CL, KP041-2ET-11CL, KP043-2ET-11CL through KP045-2ET-11CL, KP047-2ET-11CL, KP048-2ET-11CL, KP051-2ET-11CL, KP053-2ET-11CL through KP055-2ET-11CL, KP057-2ET-11CL, KP058-2ET-11CL, KP061-2ET-11CL, KP063-2ET-11CL through KP065-2ET-11CL, KP067-2ET-11CL, KP068-2ET-11CL, KP071-2ET-11CL, KP073-2ET-11CL through KP075-2ET-11CL, KP077-2ET-11CL, KP078-2ET-11CL, KP081-2ET-11CL, KP083-2ET-11CL through KP085-2ET-11CL, KP087-2ET-11CL, KP088-2ET-11CL, KP091-2ET-11CL, KP093-2ET-11CL through KP095-2ET-11CL, KP097-2ET-11CL, KP098-2ET-11CL, KP101-2ET-11CL, KP103-2ET-11CL through KP105-2ET-11CL, KP107-2ET-11CL, KP108-2ET-11CL, KP111-2ET-11CL, KP113-2ET-11CL through KP115-2ET-11CL, KP117-2ET-11CL, KP118-2ET-11CL, KP121-2ET-11CL, KP123-2ET-11CL through KP125-2ET-11CL, KP127-2ET-11CL, KP128-2ET-11CL, KP131-2ET-11CL, KP133-2ET-11CL through KP135-2ET-11CL, KP137-2ET-11CL, KP138-2ET-11CL, KP141-2ET-11CL, KP143-2ET-11CL through KP145-2ET-11CL, KP147-2ET-11CL, KP148-2ET-11CL, KP151-2ET-11CL, KP153-2ET-11CL through KP155-2ET-11CL, KP157-2ET-11CL, KP158-2ET-11CL, KP161-2ET-11CL, KP163-2ET-11CL through KP165-2ET-11CL, KP167-2ET-11CL, KP168-2ET-11CL, KP171-2ET-11CL, KP173-2ET-11CL through KP175-2ET-11CL, KP177-2ET-11CL, KP178-2ET-11CL, KP181-2ET-11CL, KP183-2ET-11CL through KP185-2ET-11CL, KP187-2ET-11CL, and KP188-2ET-11CL, in

which R_{11} is a chloro while the remainder of the substituents remain the same as the corresponding compound in Table 1;

KP001-12CL, KP002-12CL, KP004-12CL through KP007-12CL, KP008-12CL through KP012-12CL, KP014-12CL through KP017-12CL, KP018-12CL through KP022-12CL, KP024-12CL through KP027-12CL, KP028-12CL through KP032-12CL, KP034-12CL through KP037-12CL, KP038-12CL through KP042-12CL, KP044-12CL through KP047-12CL, KP048-12CL through KP052-12CL, KP054-12CL through KP057-12CL, KP058-12CL through KP062-12CL, KP064-12CL through KP067-12CL, KP068-12CL through KP072-12CL, KP074-12CL through KP077-12CL, KP078-12CL through KP082-12CL, KP084-12CL through KP087-12CL, KP088-12CL through KP092-12CL, KP094-12CL through KP097-12CL, KP098-12CL through KP102-12CL, KP104-12CL through KP107-12CL, KP108-12CL through KP112-12CL, KP114-12CL through KP117-12CL, KP118-12CL through KP122-12CL, KP124-12CL through KP127-12CL, KP128-12CL through KP132-12CL, KP134-12CL through KP137-12CL, KP138-12CL through KP142-12CL, KP144-12CL through KP147-12CL, KP148-12CL through KP152-12CL, KP154-12CL through KP157-12CL, KP158-12CL through KP162-12CL, KP164-12CL through KP167-12CL, KP168-12CL through KP172-12CL, KP174-12CL through KP177-12CL, KP178-12CL through KP182-12CL, KP184-12CL through KP187-12CL, KP188-12CL through KP190-12CL, KP001-1ET-12CL, KP002-1ET-12CL, KP004-1ET-12CL through KP007-1ET-12CL, KP008-1ET-12CL through KP012-1ET-12CL, KP014-1ET-12CL through KP017-1ET-12CL, KP018-1ET-12CL through KP022-1ET-12CL, KP024-1ET-12CL through KP027-1ET-12CL, KP028-1ET-12CL through KP032-1ET-12CL, KP034-1ET-12CL through KP037-1ET-12CL, KP038-1ET-12CL through KP042-1ET-12CL, KP044-1ET-12CL through KP047-1ET-12CL, KP048-1ET-12CL through KP052-1ET-12CL, KP054-1ET-12CL through KP057-1ET-12CL, KP058-1ET-12CL through KP062-1ET-12CL, KP064-1ET-12CL through KP067-1ET-12CL, KP068-1ET-12CL through KP072-1ET-12CL, KP074-1ET-12CL through KP077-1ET-12CL, KP078-1ET-12CL through KP082-1ET-12CL, KP084-1ET-12CL through KP087-1ET-12CL, KP088-1ET-12CL through KP092-1ET-12CL, KP094-1ET-12CL through KP097-1ET-12CL, KP098-1ET-12CL through KP102-1ET-12CL, KP104-1ET-12CL through KP107-1ET-12CL,

KP108-1ET-12CL through KP112-1ET-12CL, KP114-1ET-12CL through KP117-1ET-12CL, KP118-1ET-12CL through KP122-1ET-12CL, KP124-1ET-12CL through KP127-1ET-12CL, KP128-1ET-12CL through KP132-1ET-12CL, KP134-1ET-12CL through KP137-1ET-12CL, KP138-1ET-12CL through KP142-1ET-12CL, KP144-1ET-12CL through KP147-1ET-12CL, KP148-1ET-12CL through KP152-1ET-12CL, KP154-1ET-12CL through KP157-1ET-12CL, KP158-1ET-12CL through KP162-1ET-12CL, KP164-1ET-12CL through KP167-1ET-12CL, KP168-1ET-12CL through KP172-1ET-12CL, KP174-1ET-12CL through KP177-1ET-12CL, KP178-1ET-12CL through KP182-1ET-12CL, KP184-1ET-12CL through KP187-1ET-12CL, KP188-1ET-12CL through KP190-1ET-12CL, KP001-2ET-12CL, KP002-2ET-12CL, KP004-2ET-12CL through KP007-2ET-12CL, KP008-2ET-12CL through KP012-ET-12CL, KP014-2ET-12CL through KP017-2ET-12CL, KP018-2ET-12CL through KP022-2ET-12CL, KP024-2ET-12CL through KP027-2ET-12CL, KP028-2ET-12CL through KP032-2ET-12CL, KP034-2ET-12CL through KP037-2ET-12CL, KP038-2ET-12CL through KP042-2ET-12CL, KP044-2ET-12CL through KP047-2ET-12CL, KP048-2ET-12CL through KP052-2ET-12CL, KP054-2ET-12CL through KP057-2ET-12CL, KP058-2ET-12CL through KP062-2ET-12CL, KP064-2ET-12CL through KP067-2ET-12CL, KP068-2ET-12CL through KP072-2ET-12CL, KP074-2ET-12CL through KP077-2ET-12CL, KP078-2ET-12CL through KP082-2ET-12CL, KP084-2ET-12CL through KP087-2ET-12CL, KP088-2ET-12CL through KP092-2ET-12CL, KP094-2ET-12CL through KP097-2ET-12CL, KP098-2ET-12CL through KP102-2ET-12CL, KP104-2ET-12CL through KP107-2ET-12CL, KP108-2ET-12CL through KP112-2ET-12CL, KP114-2ET-12CL through KP117-2ET-12CL, KP118-2ET-12CL through KP122-2ET-12CL, KP124-2ET-12CL through KP127-2ET-12CL, KP128-2ET-12CL through KP132-2ET-12CL, KP134-2ET-12CL through KP137-2ET-12CL, KP138-2ET-12CL through KP142-2ET-12CL, KP144-2ET-12CL through KP147-2ET-12CL, KP148-2ET-12CL through KP152-2ET-12CL, KP154-2ET-12CL through KP157-2ET-12CL, KP158-2ET-12CL through KP162-2ET-12CL, KP164-2ET-12CL through KP167-2ET-12CL, KP168-2ET-12CL through KP172-2ET-12CL, KP174-2ET-12CL through KP177-2ET-12CL, KP178-2ET-12CL through KP182-2ET-12CL, KP184-2ET-12CL through KP187-2ET-12CL, and KP188-2ET-12CL through KP190-2ET-12CL, in

which R_{12} is a chloro while the remainder of the substituents remain the same as the corresponding ompound in Table 1;

KP001-13CL through KP003-13CL, KP005-13CL through KP007-13CL, KP009-13CL through KP013-13CL, KP015-13CL through KP017-13CL, KP019-13CL through KP023-13CL, KP025-13CL through KP027-13CL, KP029-13CL through KP033-13CL, KP035-13CL through KP037-13CL, KP039-13CL through KP043-13CL, KP045-13CL through KP047-13CL, KP049-13CL through KP053-13CL, KP055-13CL through KP057-13CL, KP059-13CL through KP063-13CL, KP065-13CL through KP067-13CL, KP069-13CL through KP073-13CL, KP075-13CL through KP077-13CL, KP07913CL through KP083-13CL, KP085-13CL through KP087-13CL, KP089-13CL through KP093-13CL, KP095-13CL through KP097-13CL, KP099-13CL through KP103-13CL, KP105-13CL through KP107-13CL, KP109-13CL through KP113-13CL, KP115-13CL through KP117-13CL, KP119-13CL through KP123-13CL, KP125-13CL through KP127-13CL, KP129-13CL through KP133-13CL, KP135-13CL through KP137-13CL, KP139-13CL through KP143-13CL, KP145-13CL through KP147-13CL, KP149-13CL through KP153-13CL, KP155-13CL through KP157-13CL, KP159-13CL through KP163-13CL, KP165-13CL through KP167-13CL, KP169-13CL through KP173-13CL, KP175-13CL through KP177-13CL, KP179-13CL through KP183-13CL, KP185-13CL through KP187-13CL, KP189-13CL, KP190-13CL, KP001-1ET-13CL through KP003-1ET-13CL, KP005-1ET-13CL through KP007-1ET-13CL, KP009-1ET-13CL through KP013-1ET-13CL, KP015-1ET-13CL through KP017-1ET-13CL, KP019-1ET-13CL through KP023-1ET-13CL, KP025-1ET-13CL through KP027-1ET-13CL, KP029-1ET-13CL through KP033-1ET-13CL, KP035-1ET-13CL through KP037-1ET-13CL, KP039-1ET-13CL through KP043-1ET-13CL, KP045-1ET-13CL through KP047-1ET-13CL, KP049-1ET-13CL through KP053-1ET-13CL, KP055-1ET-13CL through KP057-1ET-13CL, KP059-1ET-13CL through KP063-1ET-13CL, KP065-1ET-13CL through KP067-1ET-13CL, KP069-1ET-13CL through KP073-1ET-13CL, KP075-1ET-13CL through KP077-1ET-13CL, KP0791ET-13CL through KP083-1ET-13CL, KP085-1ET-13CL through KP087-1ET-13CL, KP089-1ET-13CL through KP093-1ET-13CL, KP095-1ET-13CL through KP097-1ET-13CL, KP099-1ET-13CL through KP103-1ET-13CL, KP105-1ET-13CL through KP107-1ET-13CL,

KP109-1ET-13CL through KP113-1ET-13CL, KP115-1ET-13CL through KP117-1ET-13CL, KP119-1ET-13CL through KP123-1ET-13CL, KP125-1ET-13CL through KP127-1ET-13CL, KP129-1ET-13CL through KP133-1ET-13CL, KP135-1ET-13CL through KP137-1ET-13CL, KP139-1ET-13CL through KP143-1ET-13CL, KP145-1ET-13CL through KP147-1ET-13CL, KP149-1ET-13CL through KP153-1ET-13CL, KP155-1ET-13CL through KP157-1ET-13CL, KP159-1ET-13CL through KP163-1ET-13CL, KP165-1ET-13CL through KP167-1ET-13CL, KP169-1ET-13CL through KP173-1ET-13CL, KP175-1ET-13CL through KP177-1ET-13CL, KP179-1ET-13CL through KP183-1ET-13CL, KP185-1ET-13CL through KP187-1ET-13CL, KP189-1ET-13CL, KP190-1ET-13CL, KP001-2ET-13CL through KP003-2ET-13CL, KP005-2ET-13CL through KP007-2ET-13CL, KP009-2ET-13CL through KP013-2ET-13CL, KP015-2ET-13CL through KP017-2ET-13CL, KP019-2ET-13CL through KP023-2ET-13CL, KP025-2ET-13CL through KP027-2ET-13CL, KP029-2ET-13CL through KP033-2ET-13CL, KP035-2ET-13CL through KP037-2ET-13CL, KP039-2ET-13CL through KP043-2ET-13CL, KP045-2ET-13CL through KP047-2ET-13CL, KP049-2ET-13CL through KP053-2ET-13CL, KP055-2ET-13CL through KP057-2ET-13CL, KP059-2ET-13CL through KP063-2ET-13CL, KP065-2ET-13CL through KP067-2ET-13CL, KP069-2ET-13CL through KP073-2ET-13CL, KP075-2ET-13CL through KP077-2ET-13CL, KP0792ET-13CL through KP083-2ET-13CL, KP085-2ET-13CL through KP087-2ET-13CL, KP089-2ET-13CL through KP093-2ET-13CL, KP095-2ET-13CL through KP097-2ET-13CL, KP099-2ET-13CL through KP103-2ET-13CL, KP105-2ET-13CL through KP107-2ET-13CL, KP109-2ET-13CL through KP113-2ET-13CL, KP115-2ET-13CL through KP117-2ET-13CL, KP119-2ET-13CL through KP123-2ET-13CL, KP125-2ET-13CL through KP127-2ET-13CL, KP129-2ET-13CL through KP133-2ET-13CL, KP135-2ET-13CL through KP137-2ET-13CL, KP139-2ET-13CL through KP143-2ET-13CL, KP145-2ET-13CL through KP147-2ET-13CL, KP149-2ET-13CL through KP153-2ET-13CL, KP155-2ET-13CL through KP157-2ET-13CL, KP159-2ET-13CL through KP163-2ET-13CL, KP165-2ET-13CL through KP167-2ET-13CL, KP169-2ET-13CL through KP173-2ET-13CL, KP175-2ET-13CL through KP177-2ET-13CL, KP179-2ET-13CL through KP183-2ET-13CL, KP185-2ET-13CL through KP187-2ET-13CL, KP189-2ET-13CL, and KP190-2ET-13CL, in which

R_{13} is a chloro while the remainder of the substituents remain the same as the corresponding compound in Table 1.

II. Methods of Modulating Protein Function

[0053] In another aspect, the present invention relates to a method of modulating at least one peroxisome proliferator-activated receptor (PPAR) function comprising the step of contacting the PPAR with a compound of Formula I, as described herein. The change in cell phenotype, cell proliferation, activity of the PPAR, or binding of the PPAR with a natural binding partner may be monitored. Such methods may be modes of treatment of disease, biological assays, cellular assays, biochemical assays, or the like.

[0054] The term "modulate" refers to the ability of a compound of the invention to alter the function of a PPAR. A modulator may activate the activity of a PPAR, may activate or inhibit the activity of a PPAR depending on the concentration of the compound exposed to the PPAR, or may inhibit the activity of a PPAR. The term "modulate" also refers to altering the function of a PPAR by increasing or decreasing the probability that a complex forms between a PPAR and a natural binding partner. A modulator may increase the probability that such a complex forms between the PPAR and the natural binding partner, may increase or decrease the probability that a complex forms between the PPAR and the natural binding partner depending on the concentration of the compound exposed to the PPAR, and or may decrease the probability that a complex forms between the PPAR and the natural binding partner.

[0055] The term "activate" refers to increasing the cellular function of a PPAR. The term "inhibit" refers to decreasing the cellular function of a PPAR. The PPAR function may be the interaction with a natural binding partner or catalytic activity.

[0056] The term "monitoring" refers to observing the effect of adding the compound of the invention to the cells of the method. The effect can be manifested in a change in cell phenotype, cell proliferation, PPAR activity, or in the interaction between a PPAR and a natural binding partner. Of course, the term "monitoring" includes detecting whether a change has in fact occurred or not.

[0057] The term "cell phenotype" refers to the outward appearance of a cell or tissue or the function of the cell or tissue. Examples of cell or tissue phenotype are cell size (reduction or enlargement), cell proliferation (increased or decreased numbers of cells), cell differentiation (a change or absence of a change in cell shape), cell survival, apoptosis (cell death), or the utilization of a metabolic nutrient (e.g., glucose uptake). Changes or the absence of changes in cell phenotype are readily measured by techniques known in the art.

[0058] The term "cell proliferation" refers to the rate at which a group of cells divides. The number of cells growing in a vessel can be quantified by a person skilled in the art when that person visually counts the number of cells in a defined area using a common light microscope. Alternatively, cell proliferation rates can be quantified by laboratory apparatae that optically measure the density of cells in an appropriate medium.

[0059] The term "contacting" as used herein refers to bringing a compound of this invention and a target PPAR together in such a manner that the compound can affect the activity of the PPAR, either directly; i.e., by interacting with the PPAR itself, or indirectly; i.e., by interacting with another molecule on which the activity of the PPAR is dependent. Such "contacting" can be accomplished in a test tube, a petri dish or the like. In a test tube, contacting may involve only a compound and a PPAR of interest or it may involve whole cells. Cells may also be maintained or grown in cell culture dishes and contacted with a compound in that environment. In this context, the ability of a particular compound to affect a PPAR related disorder; i.e., the IC_{50} of the compound can be determined before use of the compounds in vivo with more complex living organisms is attempted. For cells outside the organism, multiple methods exist, and are well-known to those skilled in the art, to get the PPARs in contact with the compounds including, but not limited to, direct cell microinjection and numerous transmembrane carrier techniques.

[0060] In certain embodiments, the PPAR may be selected from the group consisting of PPARα, PPARδ, and PPARγ.

III. Target Diseases to be Treated

[0061] In another aspect, the present invention relates to a method of treating a disease comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Formula I, as described herein, to the patient.

[0062] The term "therapeutically effective amount" as used herein refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of diabetes or dyslipidemia a therapeutically effective amount refers to that amount which has the effect of (1) reducing the blood glucose levels; (2) normalize lipids, e.g. triglycerides, low-density lipoprotein; (3) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with the disease to be treated.

[0063] Biological processes modulated by PPAR are those modulated by receptors, or receptor combinations, which are responsive to the PPAR receptor ligands described herein. These processes include. for example, plasma lipid transport and fatty acid catabolism, regulation of insulin sensitivity and blood glucose levels, which are involved in hypoglycemia/hyperinsulinemia (resulting from, for example, abnormal pancreatic beta cell function, insulin secreting tumors and/or autoimmune hypoglycemia due to autoantibodies to insulin, the insulin receptor, or autoantibodies that are stimulatory to pancreatic beta cells), macrophage differentiation which lead to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, and adipocyte differentiation.

[0064] Non-insulin-dependent diabetes mellitus (NIDDM), or Type 2 diabetes, is the more common form of diabetes, with 90-95% of hyperglycemic patients experiencing this form of the disease. Resistance to the metabolic actions of insulin is one of the key features of non-insulin dependent diabetes (NIDDM). Insulin resistance is characterized by impaired uptake and utilization of glucose in insulin-sensitive target organs, for example, adipocytes and skeletal muscle, and by impaired inhibition of hepatic glucose output. The functional insulin deficiency and the failure of insulin to suppress hepatic glucose output results in fasting hyperglycemia. Pancreatic β-cells compensate for the insulin resistance by secreting increased levels of insulin. However, the β-cells are unable to maintain this high output of insulin, and, eventually, the glucose-induced insulin secretion falls, leading to the deterioration of glucose homeostasis and to the subsequent development of overt diabetes.

[0065] Compelling evidence has shown that PPARγ is a valuable molecular target for development of drugs for treatment of insulin resistance (see Willson, et al. J. Med. Chem. 43: 527-550 (2000)). In fact, PPARγ agonists rosiglitazone (Avandia) and pioglitazone (Actos) are insulin sensitizers and are currently marketed drugs for treatment of type 2 diabetes.

[0066] Obesity is an excessive accumulation of adipose tissue. Recent work in this area indicates that PPARγ plays a central role in the adipocyte gene expression and differentiation. Excess adipose tissue is associated with the development of serious medical conditions, for example, non-insulin-dependent diabetes mellitus (NIDDM), hypertension, coronary artery disease, hyperlipidemia obesity and certain malignancies. The adipocyte may also influence glucose homeostasis through the production of tumor necrosis factor α (TNFα) and other molecules. PPARγ activators, in particular Troglitazone®, have been found to convert cancerous tissue to normal cells in liposarcoma, a tumor of fat (PNAS 96:3951-3956, 1999). Therefore, PPARγ activators may be useful in the treatment of obesity and breast and colon cancer.

[0067] Moreover, PPARγ activators, for example Troglitazone®, have been implicated in the treatment of polycystic ovary syndrome (PCO). This is a syndrome in women that is characterized by chronic anovulation and hyperandrogenism. Women with this syndrome often have insulin resistance and an increased risk for the development of non insulin-dependent diabetes mellitus. (Dunaif, Scott, Finegood, Quintana, Whitcomb, J. Clin. Endocrinol. Metab., 81:3299,1996.

[0068] Furthermore, PPARγ activators have recently been discovered to increase the production of progesterone and inhibit steroidogenesis in granulosa cell cultures and therefore may be useful in the treatment of climacteric. (USP 5,814,647 Urban et al. September 29,1998; B. Lohrke et al. Journal of Edocrinology, 159,429-39, 1998). Climacteric is defined as the syndrome of endocrine, somatic and psychological changes occurring at the termination of the reproductive period in the female.

[0069] PPARα is activated by a number of medium and long-chain fatty acids and is involved in stimulating β-oxidation of fatty acids in tissues such as liver, heart, skeletal muscle, and brown adipose tissue (Isseman and Green, supra; Beck et al., Proc. R. Soc. Lond.

247:83-87,1992; Gottlicher et al., Proc. Natl. Acad. Sci. USA 89:4653-4657, 1992). Pharmacological PPARα activators, for example fenofibrate, clofibrate, genfibrozil, and bezafibrate. are also involved in substantial reduction in plasma triglycerides along with moderate reduction in LDL cholesterol, and they are used particularly for the treatment of hypertriglyceridemia, hyperlipidemia and obesity. PPARα is also known to be involved in inflammatory disorders. (Schoonjans, K., Current Opinion in Lipidology, 8, 159-66, 1997).

[0070] PPARα agonists may also be useful in raising HDL levels and therefore may be useful in treating atherosclerotic diseases. (Leibowitz et al.; WO/9728149). Atherosclerotic diseases include vascular disease, coronary heart disease, cerebrovascular disease and peripheral vessel disease. Coronary heart disease includes CHD death, myocardial infarction, and coronary revascularization. Cerebrovascular disease includes ischemic or hemorrhagic stroke and transient ischemic attacks.

[0071] The third subtype of PPARs, PPARδ (PPARβ, NUC1), is broadly expressed in the body and has been shown to be a valuable molecular target for treatment of dyslipedimia and other diseases. For example, in a recent study in insulin-resistant obese rhesus monkeys, a potent and selective PPARδ compound was shown to decrease VLDL and increase HDL in a dose response manner (Oliver et al., Proc. Natl. Acad. Sci. U. S. A.98: 5305, 2001).

[0072] Compounds described herein may be activating both PPARα and PPARγ, or PPARδ and PPARγ, or all three PPAR subtypes and therefore may be used in the treatment of dyslipidemia associated with atherosclerosis, non-insulin dependent diabetes mellitus, Syndrome X,. (Staels, B. et al., Curr. Pharm. Des., 3 (1),1-14 (1997» and familial combined hyperlipidemia (FCH). Syndrome X is the syndrome characterized by an initial insulin resistant state, generating hyperinsulinaemia, dyslipidaemia and impaired glucose tolerance, which can progress to non-insulin dependent diabetes mellitus (Type 2 diabetes), characterized by hyperglycemia. FCH is characterized by hypercholesterolemia and hypertriglyceridemia within the same patient and family.

[0073] Thus, in certain embodiments, the disease to be treated by the methods of the present invention is selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders

associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury.

IV. Pharmaceutical Compositions

[0074] In another aspect, the present invention relates to a pharmaceutical composition comprising a compound of Formula I, as described herein, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0075] The term "pharmaceutical composition" refers to a mixture of a compound of the invention with other chemical components, such as carriers, diluents or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0076] The term "carrier" refers to relatively nontoxic chemical compounds or agents. Such carriers may facilitate the incorporation of a compound into cells or tissues. For example, human serum albumin (HSA) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

[0077] The term "diluent" refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents can also be used to stabilize compounds because they can provide a more stable environment. Salts dissolved in buffered solutions (providing pH control) are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline. It is a buffer found naturally in the blood system. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

[0078] The term "physiologically acceptable" refers to a carrier or diluent that does not abrogate the biological activity or properties of the compound, and is nontoxic.

[0079] The compounds described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," 20th ed. Edited by Alfonso Gennaro, 2000.

a) Routes Of Administration

[0080] Suitable routes of administration may, for example, include oral, rectal, transmucosal, pulmonary, ophthalmic or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

[0081] Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

b) Composition/Formulation

[0082] The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0083] Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

[0084] For intravenous injections, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For other parenteral injections, the agents of the invention may be formulated in aqueous or nonaqueous solutions, preferably with physiologically compatible buffers or excipients. Such excipients are generally known in the art.

[0085] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers or excipients well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more compound of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0086] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0087] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[0088] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in conventional manner.

[0089] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0090] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0091] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium

carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0092] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0093] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[0094] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0095] A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a 10% ethanol, 10% polyethylene glycol 300, 10% polyethylene glycol 40 castor oil (PEG-40 castor oil) with 70% aqueous solution. This cosolvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a cosolvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the cosolvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of PEG-40 castor oil, the fraction size of polyethylene glycol 300 may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides maybe included in the aqueous solution.

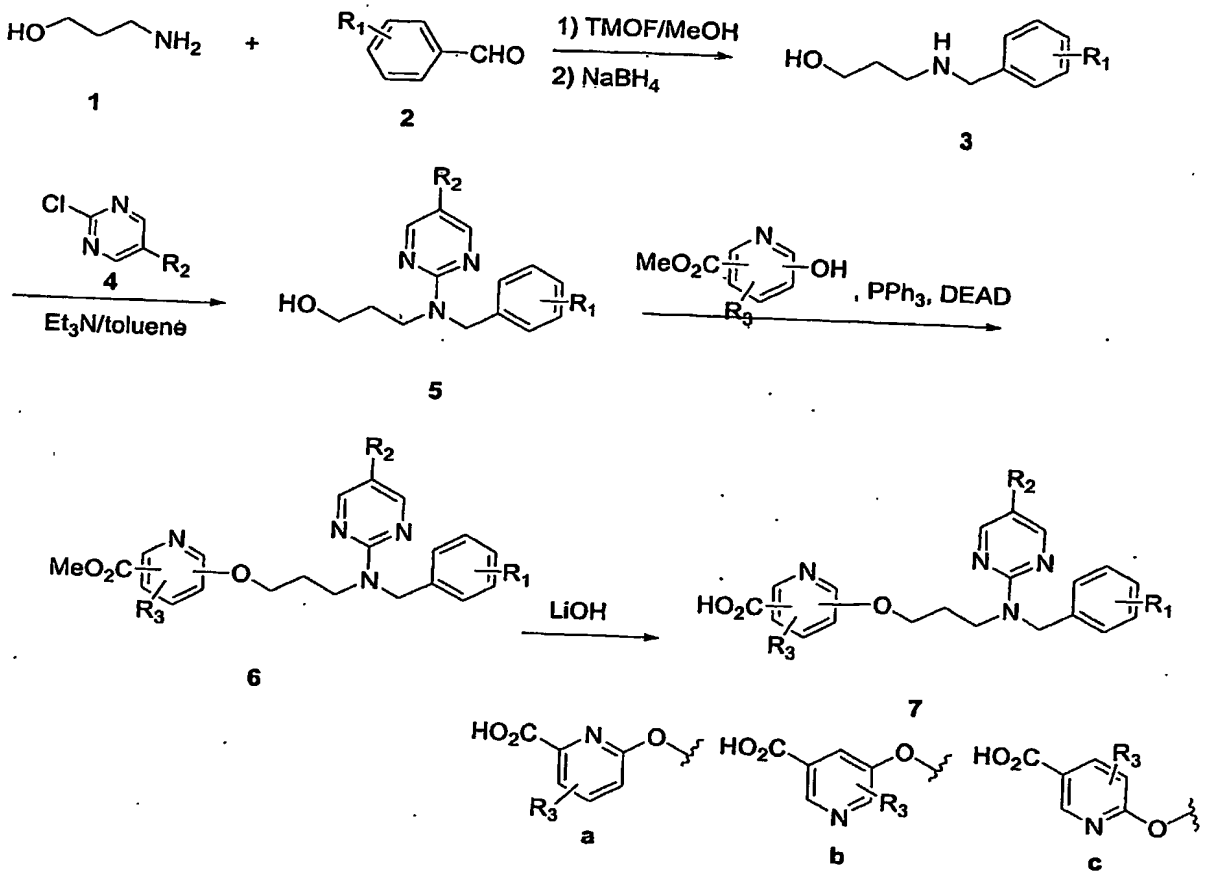
[0096] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as N-methylpyrrolidone also may be employed, although usually at the cost of greater toxicity.

Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0097] Many of the compounds of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acid or base forms.

V. Synthesis of the Compounds of the Invention

[0098] Compounds of the present invention can be synthesized using standard synthetic techniques known to those of skill in the art. Some of the compounds of the present invention can be synthesized using the general synthetic procedures set forth below, in Scheme 1. Additional synthetic procedures are set forth in the Examples below.



SCHEME 1

Examples

[0099] The invention will now be described in greater detail by reference to the following non-limiting examples.

Example 1: Typical procedure for synthesis of intermediate 5 (3-[(2,4-Bis-trifluoromethyl-benzyl)-(5-ethyl-pyrimidin-2-yl)-amino]-propan-1-ol).

[0100] 3-Hydroxypropylamine (5.62 mL, 73.5 mmol, 1.2 equiv.) was dissolved in 250 mL of TMOF/MeOH (1:5) (TMOF = trimethyl orthoformate) and then 2,4-bis(trifluoromethyl)benzaldehyde (14.83g, 61.2 mmol, 1.0 equiv.) was added to this solution at room temperature with stirring. The resulting solution was stirred at rt for 6 hours and then

cooled to 0°C. $NaBH_4$ was added to the cooled reaction solution in portions with vigorously stirring. After TLC indicated the reduction complete, the reaction mixture was concentrated on rotavapor under reduced pressure. The residue was diluted with 250 mL of ethyl acetate and washed with water, brine and then dried over Na_2SO_4. After removal of solvent, 17.1 g (93% yield) colorless oil was obtained as desired N-2,5-bis(trifluoromethyl)benzyl-3-hydroxypropylamine (3). ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.9 (s, 1H), 7.75 (m, 2H), 4.0 (s, 2H), 3.8 (t, 2H), 2.85 (t, 2H), 1.76 (m, 2H).

[0101] To a 150 mL of high pressure flask was added intermediate (3) (12.23g, 40.6 mmol, 1.0 equiv.), 2-chloro-5-ethylpyrimidine (4.9 mL, 40.6 mmol, 1.0 equiv.), triethylamine (11.3 mL, 81.2 mmol, 2.0 equiv.) and 50 mL of toluene. After the flask was sealed, it was heated to 180°C with stirring. After reaction at same temperature for 48 hours, the reaction mixture was cooled to room temperature and then diluted with 100 mL of ethyl acetate. The resulting solution was washed with water, brine and the dried over Na_2SO_4. After removal of solvent, the residue was purified by chromatography to give 7,7 g (46% yield) of product (5) as bright brown solid. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.15 (s, 2H), 7.90 (s, 1H), 7.67 (d, 1H), 7.30 (d, 1H), 5.02 (s, 2H), 3.71 (m, 2H), 3.53 (m, 2H), 2.42 (q, 2H), 1.75 (m, 2H), 1.15 (t, 3H).

Example 2: Typical procedure for synthesis of 7 (6-{3-[(2,4-Bis-trifluoromethyl-benzyl)-(5-ethyl-pyrimidin-2-yl)-amino]-propoxy}-pyridine-2-carboxylic acid).

[0102] Alcohol (5) (4.85 g, 11.9 mmol) and tripenylphosphine (4.68 g, 17.8 mmol) were dissolved in 115 mL of dichloromethane as stock solution. Phenol substrates (each: 0.77 mmol, 1.5 equiv) were charged in different reaction vials, respectively. To each of the reaction vials was added 5 mL of the above stock solution (captaining 1.0 equiv of alcohol (5) and 1.5 equiv of PPh_3) followed by diisopropyl azodicarboxylate (154 μL, 1.5 equiv). The resulting reaction solutions were stirred at room temperature for 1.5 hours and then concentrated under N_2 blow. The residues were purified by chromatography to give 15 desired methyl ester products.

[0103] Hydrolysis of the methyl esters by treatment with 1 N LiOH in THF/MeOH (3:1) solution gave corresponding acids.

[0104] ^{1}H NMR for (**7a**, R_3 = H) (400 MHz, DMSO), δ (ppm): 8.19 (s, 2H), 7.9 (m, 2H), 7.75 (m, 1H), 7.55 (d, 1H), 7.4 (d, 1H), 6.82 (d, 1H), 5.05 (s, 2H), 4.3 (m, 2H), 3.75 (m, 2H), 2.4 (q, 2H), 2.07 (m, 2H), 1.1 (t, 3H).

[0105] ^{1}H NMR for (**7b**, R_3 = H) (400 MHz, $CDCL_3$), δ (ppm): 8.92 (S, 1H), 8.50 (s, 1H), 8.20 (s, 2H), 7.92 (s, 1H), 7.83 (s, 1H), 7.72 (d, 1H), 7.41 (d, 1H), 5.19 (s, 1H), 4.15 (m, 2H), 3.85 (m, 2H), 2.5 (q, 2H), 2.1 (m, 2H), 1.16 (t, 3H).

[0106] ^{1}H NMR for (**7c**, R_3 = 3-Cl) (400 MHz, $CDCL_3$), δ (ppm): 8.70 (S, 1H), 8.20 (s, 1H), 8.15 (s, 2H), 7.90 (s, 1H), 7.70 (d, 1H), 7.41 (d, 1H), 5.19 (s, 1H), 4.40 (t, 2H), 3.80 (t, 2H), 2.5 (q, 2H), 2.20 (m, 2H), 1.20 (t, 3H).

Example 3: Biological activity.

[0107] The compounds were evaluated in a cell-based assay to determine their human PPAR activity. The plasmids for human PPAR-GAL4 chimeras were prepared by fusing amplified cDNAs encoding the LBDs of PPARs to the C-terminal end of the yeast GAL4 DNA binding domain. CV-1 cells were grown and transiently tranfected with PerFectin (GTS, San Diego, CA) according to the manufacturer's protocol along with a luciferase reporter. Eight hours after transfection, 50 µl of cells were replated into 384 well plates ($1X10^5$ cells/well). Sixteen hours after replating, cells were treated with either compounds or 1% DMSO for 24 hours. Luciferase activity was then assayed with Britelite (Perkin Elmer) following the manufacturer's protocol and measured with either the Perkin Elmer Viewlux or Molecular Devices Acquest.

Table 2. Biological activity of compounds **7**.

Compounds				EC_{50}		
	R_1	R_2	R_3	hPPARα	hPPARγ	hPPARδ
7a	2,4-di-CF_3	Et	H	2.2 µM	71 nM	> 100 µM
7b	2,4-di-CF_3	Et	H	580 nM	314 nM	16 µM
7c	2,4-di-CF_3	Et	3-Cl	> 100 µM	938 nM	> 100 µM

[0108] Thus, those of skill in the art will appreciate that the compounds and uses disclosed herein can be used as PPAR modulators, providing a therapeutic effect.

[0109] One skilled in the art will appreciate that these methods and compounds are and may be adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods, procedures, and compounds described herein are presently representative of preferred embodiments and are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention and are defined by the scope of the claims.

[0110] It will be apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

[0111] Those skilled in the art recognize that the aspects and embodiments of the invention set forth herein may be practiced separate from each other or in conjunction with each other. Therefore, combinations of separate embodiments are within the scope of the invention as claimed herein.

[0112] All patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

[0113] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions indicates the exclusion of equivalents of the features shown and described or portions thereof. It is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has

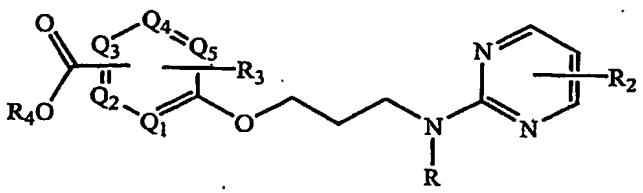
been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

[0114] In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described.

[0115] Other embodiments are within the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I

(I) 

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

One of Q_1 - Q_5 is nitrogen and the rest are carbon, wherein said carbon is optionally substituted with hydrogen, R_3, or $-C(O)OR_4$;

R_1 - R_3 are each independently selected from the group consisting of

a) hydrogen;

b) alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino;

c) a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of

A) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

B) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; and

n1 is 0 or 1;

C) halogen or perhaloalkyl;

D) cyano;

E) nitro;

F) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

d) perhaloalkyl; and

e) halogen; and

R_4 is selected from the group consisting of hydrogen and lower alkyl.

2. The compound of Claim 1, wherein R_1 is alkyl, optionally substituted with one or more optionally substituted carbocyclic or heterocyclic rings.

3. The compound of Claim 2, wherein said alkyl is a lower alkyl.

4. The compound of Claim 3, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl.

5. The compound of Claim 2, wherein said carbocyclic ring phenyl.

6. The compound of Claim 5, wherein said phenyl is optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino.

7. The compound of Claim 6, wherein said substituent is perhaloalkyl.

8. The compound of Claim 7, wherein said perhaloalkyl is trifluoromethyl.

9. The compound of Claim 1, wherein R_1 is 2,4-bis(trifluoromethyl)phenyl.

10. The compound of Claim 1, wherein R_2 is optionally substituted alkyl.

11. The compound of Claim 10, wherein said alkyl is a lower alkyl.

12. The compound of Claim 11, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl.

13. The compound of Claim 1, wherein R_2 is ethyl.

14. The compound of Claim 1, wherein R_3 is hydrogen, halogen, or optionally substituted alkyl.

15. The compound of Claim 14, wherein said alkyl is a lower alkyl.

16. The compound of Claim 15, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl.

17. The compound of Claim 1, wherein R_3 is methyl.

18. The compound of Claim 1, wherein R_3 is hydrogen.

19. The compound of Claim 1, wherein R_3 is halogen, selected from the group consisting of fluoro, chloro, bromo, and iodo.

20. The compound of Claim 1, wherein R_3 is chloro.

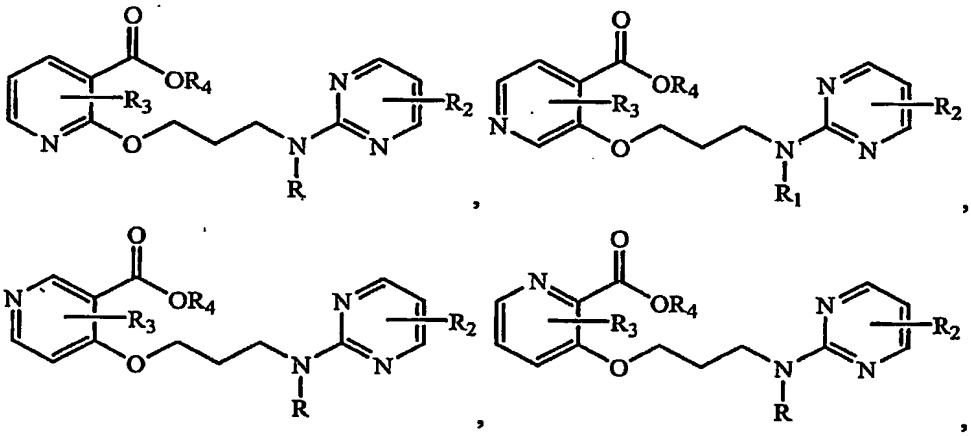
21. The compound of Claim 1, wherein R_4 is hydrogen or optionally substituted alkyl.

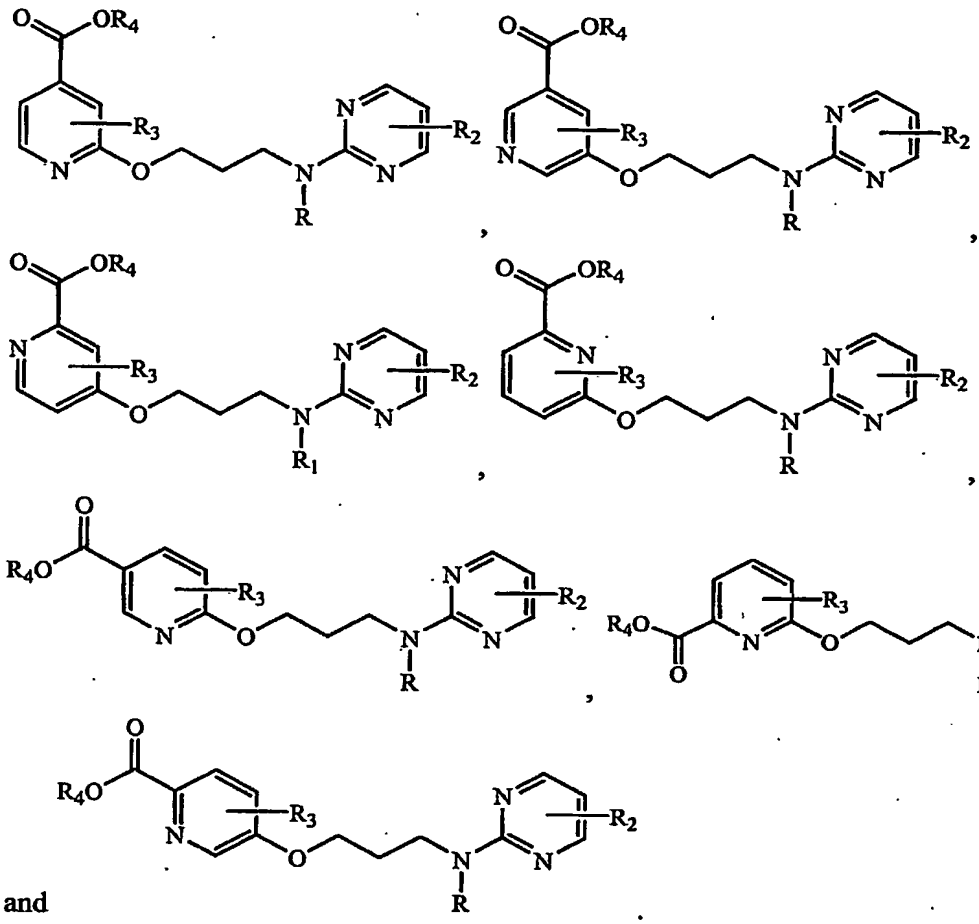
22. The compound of Claim 21, wherein said alkyl is a lower alkyl.

23. The compound of Claim 22, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl.

24. The compound of Claim 1, wherein R_4 is hydrogen.

25. The compound of Claim 1 selected from the group consisting of





and

26. A compound selected from the group consisting of KP001 through KP190, KP001-1ET through KP190-1ET, KP001-2ET through KP190-2ET, KP006-9CL through KP008-9CL, KP010-9CL, KP016-9CL through KP018-9CL, KP020-9CL, KP026-9CL through KP028-9CL, KP030-9CL, KP036-9CL through KP038-9CL, KP040-9CL, KP046-9CL through KP048-9CL, KP050-9CL, KP056-9CL through KP058-9CL, KP060-9CL, KP066-9CL through KP068-9CL, KP070-9CL, KP076-9CL through KP078-9CL, KP080-9CL, KP086-9CL through KP088-9CL, KP090-9CL, KP096-9CL through KP098-9CL, KP100-9CL, KP106-9CL through KP108-9CL, KP110-9CL, KP116-9CL through KP118-9CL, KP120-9CL, KP126-9CL through KP128-9CL, KP130-9CL, KP136-9CL through KP138-9CL, KP140-9CL, KP146-9CL through KP148-9CL, KP150-9CL, KP156-9CL through KP158-9CL, KP160-9CL, KP166-9CL through KP168-9CL, KP170-9CL, KP176-9CL through KP178-9CL, KP180-9CL, KP186-9CL through KP188-9CL, KP190-9CL,

KP006-1ET-9CL through KP008-1ET-9CL, KP010-1ET-9CL, KP016-1ET-9CL through KP018-1ET-9CL, KP020-1ET-9CL, KP026-1ET-9CL through KP028-1ET-9CL, KP030-1ET-9CL, KP036-1ET-9CL through KP038-1ET-9CL, KP040-1ET-9CL, KP046-1ET-9CL through KP048-1ET-9CL, KP050-1ET-9CL, KP056-1ET-9CL through KP058-1ET-9CL, KP060-1ET-9CL, KP066-1ET-9CL through KP068-1ET-9CL, KP070-1ET-9CL, KP076-1ET-9CL through KP078-1ET-9CL, KP080-1ET-9CL, KP086-1ET-9CL through KP088-1ET-9CL, KP090-1ET-9CL, KP096-1ET-9CL through KP098-1ET-9CL, KP100-1ET-9CL, KP106-1ET-9CL through KP108-1ET-9CL, KP110-1ET-9CL, KP116-1ET-9CL through KP118-1ET-9CL, KP120-1ET-9CL, KP126-1ET-9CL through KP128-1ET-9CL, KP130-1ET-9CL, KP136-1ET-9CL through KP138-1ET-9CL, KP140-1ET-9CL, KP146-1ET-9CL through KP148-1ET-9CL, KP150-1ET-9CL, KP156-1ET-9CL through KP158-1ET-9CL, KP160-1ET-9CL, KP166-1ET-9CL through KP168-1ET-9CL, KP170-1ET-9CL, KP176-1ET-9CL through KP178-1ET-9CL, KP180-1ET-9CL, KP186-1ET-9CL through KP188-1ET-9CL, KP190-1ET-9CL, KP006-2ET-9CL through KP008-2ET-9CL, KP010-2ET-9CL, KP016-2ET-9CL through KP018-2ET-9CL, KP020-2ET-9CL, KP026-2ET-9CL through KP028-2ET-9CL, KP030-2ET-9CL, KP036-2ET-9CL through KP038-2ET-9CL, KP040-2ET-9CL, KP046-2ET-9CL through KP048-2ET-9CL, KP050-2ET-9CL, KP056-2ET-9CL through KP058-2ET-9CL, KP060-2ET-9CL, KP066-2ET-9CL through KP068-2ET-9CL, KP070-2ET-9CL, KP076-2ET-9CL through KP078-2ET-9CL, KP080-2ET-9CL, KP086-2ET-9CL through KP088-2ET-9CL, KP090-2ET-9CL, KP096-2ET-9CL through KP098-2ET-9CL, KP100-2ET-9CL, KP106-2ET-9CL through KP108-2ET-9CL, KP110-2ET-9CL, KP116-2ET-9CL through KP118-2ET-9CL, KP120-2ET-9CL, KP126-2ET-9CL through KP128-2ET-9CL, KP130-2ET-9CL, KP136-2ET-9CL through KP138-2ET-9CL, KP140-2ET-9CL, KP146-2ET-9CL through KP148-2ET-9CL, KP150-2ET-9CL, KP156-2ET-9CL through KP158-2ET-9CL, KP160-2ET-9CL, KP166-2ET-9CL through KP168-2ET-9CL, KP170-2ET-9CL, KP176-2ET-9CL through KP178-2ET-9CL, KP180-2ET-9CL, KP186-2ET-9CL through KP188-2ET-9CL, KP190-2ET-9CL, KP002-10CL through KP004-10CL, KP009-10CL, KP012-10CL through KP014-10CL, KP019-10CL, KP022-10CL through KP024-10CL, KP029-10CL, KP032-10CL through KP034-10CL, KP039-10CL, KP042-10CL through KP044-10CL, KP049-10CL, KP052-10CL through KP054-10CL, KP059-

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27. A method of modulating a peroxisome proliferator-activated receptor (PPAR) function comprising contacting said PPAR with a compound of Claim 1 and monitoring a change in cell phenotype, cell proliferation, activity of said PPAR, or binding of said PPAR with a natural binding partner.

28. The method of Claim 27, wherein said PPAR is selected from the group consisting of PPARα, PPARδ, and PPARγ.

29. A method of inhibiting the formation of adipocytes in a mammal comprising administering a therapeutically effective amount of a compound of Claim 1 to said mammal.

30. A method of treating a disease comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to said patient.

31. The method of Claim 30, wherein said disease is selected from the group consisting of obesity, diabetes, hyperinsulinemia, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury.

32. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable diluent, excipient, or carrier.

PYRIDINE COMPOUNDS AS MODULATORS OF PPAR AND METHODS OF TREATING METABOLIC DISORDERS

Abstract of the Disclosure

Compounds as modulators of peroxisome proliferator activated receptors, pharmaceutical compositions comprising the same, and methods of treating disease using the same are disclosed.

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